BMJ

RESEARCH

Fetal growth in early pregnancy and risk of delivering low birth weight infant: prospective cohort study

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doi: 10.1136/bmj.39129.637917.AE

ABSTRACT

Objective To determine if first trimester fetal growth is associated with birth weight, duration of pregnancy, and the risk of delivering a small for gestational age infant.

Design Prospective cohort study of 38 033 pregnancies between 1999 and 2003.

Setting 15 centres representing major regions of the United States.

Participants 976 women from the original cohort who conceived as the result of assisted reproductive technology, had a first trimester ultrasound measurement of fetal crown-rump length, and delivered live singleton infants without evidence of chromosomal or congenital abnormalities. First trimester growth was expressed as the difference between the observed and expected size of the fetus, expressed as equivalence to days of gestational age.

Main outcome measures Birth weight, duration of pregnancy, and risk of delivering a small for gestational age infant.

Results For each one day increase in the observed size of the fetus, birth weight increased by 28.2 (95% confidence interval 14.6 to 41.2) g. The association was substantially attenuated by adjustment for duration of pregnancy (adjusted coefficient 17.1 (6.6 to 27.5) g). Further adjustments for maternal characteristics and complications of pregnancy did not have a significant effect. The risk of delivering a small for gestational age infant decreased with increasing size in the first trimester (odds ratio for a one day increase 0.87, 0.81 to 0.94). The association was not materially affected by adjustment for maternal characteristics or complications of pregnancy.

Conclusion Variation in birth weight may be determined, at least in part, by fetal growth in the first 12 weeks after conception through effects on timing of delivery and fetal growth velocity.

INTRODUCTION

Low birth weight infants are at increased risk of perinatal and infant death.[1] Low birth weight is also associated with increased mortality in later life.[2] Moreover, mothers who deliver low birth weight infants have a greater than fourfold adjusted relative risk of ischaemic heart disease.[3] The factors that determine low birth weight are clearly clinically and biologically important.

Placental function in early pregnancy, as measured by circulating concentrations of placentally derived proteins in the mother's serum, is associated with risk of low birth weight.[4] Moreover, animal models suggest that periconceptional undernutrition affects the timing of birth and, hence, birth weight.[5] A single study has shown that fetuses that were smaller than expected in the first trimester (on the basis of menstrual history) were at increased risk of being low birth weight.[6] This has been interpreted as indicating that impairment of fetal growth begins in the first trimester. However, when the expected size of the fetus is based on menstrual history, a smaller than expected fetus in early pregnancy may also reflect delayed ovulation. Other authors have suggested that a prolonged menstruation-conception interval is associated with shorter duration of pregnancy and lower birth weight.[7] The uncertainty in the interpretation of existing studies relates to the inherent uncertainty in using menstrual history to estimate the date of conception. We assessed the relation between discrepancy in the observed and expected size of the fetus in the first trimester and the birth weight, duration of pregnancy, and risk of delivering a small for gestational age infant among a large cohort of women with a known date of conception.

METHODS

We studied 976 women who conceived as the result of assisted reproductive technology (in vitro fertilisation or intrauterine insemination), from a previously described prospective cohort study.[8] This prospective cohort study of screening for Down's syndrome took place at 15 US centres from October 1999 to December 2002. The inclusion criteria were a maternal age of 16 years or older, a singleton live fetus, and a fetal crown-rump length corresponding to a gestational age of 10 weeks 3 days to 13 weeks 6 days. We excluded women from the study if they had had

previous measurement of nuchal translucency or if anencephaly was diagnosed in the fetus. Out of 42 367 patients approached, we enrolled 38 033 and 1120 (3%) had conceived as a result of intrauterine insemination or in vitro fertilisation. Of these pregnancies, 14 (1.3%) resulted in miscarriage, 3 (0.3%) resulted in perinatal death, 2 (0.2%) resulted in live births with chromosomal abnormalities, and 21 (2.0%) resulted in live births with congenital abnormalities. Complete data on maternal characteristics, exposures, complications of pregnancy, and birth weights were available in 976 (90%) of the remaining pregnancies. The final study population consisted of 976 singleton pregnancies resulting in live births without evidence of chromosomal or congenital abnormalities (table 1). All participants gave written informed consent.

Table 1 | Characteristics and outcomes of pregnancies conceived as a result of assisted reproductive technology. Values are numbers (percentages) unless stated otherwise

Characteristics	Pregnancies (n=976)
Median (IQR) maternal age (years)	36.1 (32.9-39.2)
Median (IQR) maternal body mass index	23.1 (21.2-26.3)
Race/ethnicity:	
White	850 (86.7)
Hispanic	43 (4.4)
Black	21 (2.1)
Asian	64 (6.5)
Native American	1 (0.1)
Other	2 (0.2)
Education (years):	
0-8	0
9-12	44 (4.5)
13-15	137 (14.0)
≥16	800 (81.6)
Marital status:	
Married	895 (91.2)
Single	80 (8.2)
Divorced	4 (0.4)
Other	2 (0.2)
Depression	32 (3.3)
Smoking status	19 (1.9)
Previous pregnancies:	
None	431 (43.9)
Term	230 (23.5)
Preterm <37 weeks	44 (4.5)
Miscarriage	342 (34.9)
Abortion	172 (17.5)
Hypertension	7 (0.7)
Diabetes	6 (0.6)
Pre-eclampsia	39 (4.0)
Preterm labour	64 (6.5)
Assisted reproductive technology:	
Intrauterine insemination	471 (48.0)
In vitro fertilisation	510 (52.0)
Median (IQR) gestational age (days)	277 (270-283)
Median (IQR) birth weight (g)	3321 (3005-3657)
IQR=interquartile range.	

We used ultrasound to measure fetal crown-rump length before 14 weeks (between 59 and 83 days after conception). Measurement of crown-rump length has been shown to provide a precise measure of gestational age up to 14 weeks of pregnancy. Its variability in predicting menstrual age is constant in this gestational age range.[9] We related the observed size of the embryo or fetus to the expected size on the basis of the date of conception, which is precisely known for pregnancies resulting from assisted reproductive technology. The time of conception is directly observed in pregnancies resulting from in vitro fertilisation. Intrauterine insemination is timed to coincide with ovulation, which is either induced or identified by measuring luteinising hormone, so the difference between time of insemination and conception is no longer than 24-36 hours. We expressed the difference between the actual and predicted crown-rump length as the difference in days of gestation (ΔGA)—that is, the estimated post-conception age according to crown-rump length minus the actual number of days post-conception based on the assisted reproductive method. Positive ΔGA indicates a larger than expected fetus, and a negative value indicates a smaller than expected fetus.

Maternal characteristics studied were maternal age; height; weight in the first trimester; body mass index; race and ethnicity; number of previous term and preterm deliveries, miscarriages, and abortions; elevation above the sea level of the area of residence; number of completed years of education; and fetal sex. Complications of pregnancy were preterm delivery, pre-eclampsia, preterm premature rupture of the fetal membranes, preterm labour, placental abruption, and placenta praevia. We also adjusted analyses for diabetes and gestational diabetes, hypertension, smoking status and alcohol consumption, marital status, and diagnosis of depression. We defined delivery of a small for gestational age infant as birth weight below the 10th centile for gestational age.[10] We used multivariable linear regression to model birth weight and multivariable logistic regression to model the risk of delivering a small for gestational age infant. We assessed linearity with fractional polynomials up to polynomials of the fourth order.[11] We used the Wald test to assess the statistical significance of the change in ΔGA coefficient in adjusted models. We assessed goodness of fit with the Hosmer and Lemeshow test.[12] We used Stata 9.0 for analyses.

RESULTS

Birth weight varied as a linear function of ΔGA: a one day increase in ΔGA was associated with a 28.2 g increase in birth weight (table 2, fig 1). Higher order fractional polynomial models did not improve the fit. Adjustment for maternal characteristics and complications of the pregnancy had no significant effect on the association (table 2). The association between birth weight and ΔGA was significantly attenuated by adjustment for duration of pregnancy (adjusted coefficient for one day increase in ΔGA 17.1 (95% confidence interval 6.6 to 27.5) g). Adjustment for maternal

characteristics and complications of pregnancy did not further attenuate the strength of this association (adjusted coefficient 15.0 (4.6 to 25.4) g). Duration of pregnancy was also proportional to ΔGA. A one day increase in ΔGA was associated with a 0.42 day increase in duration of pregnancy (table 2). Maternal characteristics and pregnancy complications did not significantly affect the strength of this association. ΔGA explained approximately 2% of the variation in birth weight, and the combination of all factors included in the full model explained 19% ($R^2=0.02$; adjusted $R^2=0.19$).

One hundred and thirteen (11.5%) small for gestational age infants were born. The risk of delivering a small for gestational age infant varied inversely with first trimester growth (fig 2). A one day increase in ΔGA was associated with a 13% reduction in the odds of delivering a small for gestational age infant (table 2). The relation was best described by a linear function. Higher order fractional polynomial models did not improve the fit. Adjustment for maternal characteristics and complications of pregnancy did not significantly affect the probability of delivering a small for gestational age infant (table 2). The area under the

receiver operating characteristics curve of ΔGA as a predictor of delivery of a small for gestational age infant was 0.73 after adjustment for confounders. Gestational age at the time of ultrasonography did not have a significant effect on the associations between ΔGA and birth weight (P=0.9) or on the risk of delivering a small for gestational age infant (P=0.3).

DISCUSSION

First trimester growth

Our main finding was that the size of the fetus in the first trimester of pregnancy was associated with the birth weight. Approximately half of this association was due to the effect of first trimester size on the duration of pregnancy. The clinical significance of this finding is underlined by the association between fetal growth in early pregnancy and the risk of delivering a small for gestational age infant. Before the widespread use of ultrasound, fetal growth was thought to be largely genetically determined in early pregnancy and variation in fetal growth was thought to be primarily a feature of the second half of pregnancy.[13] With the widespread clinical use of ultrasound, analysis of
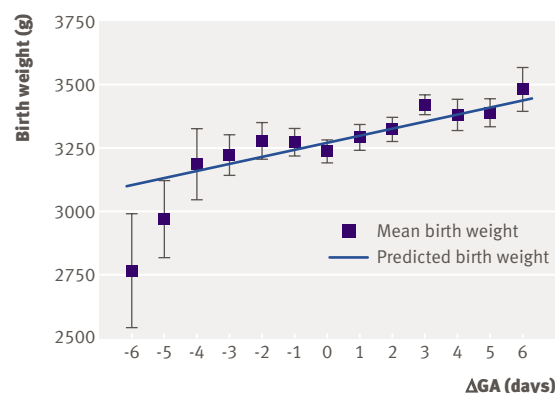

Fig 1 | Birth weight as a function of ΔGA (difference between observed and expected size of fetus in first trimester of pregnancy). Mean (±SE) birth weights and fitted values from multivariable linear regression are plotted for each day of ΔGA discrepancy
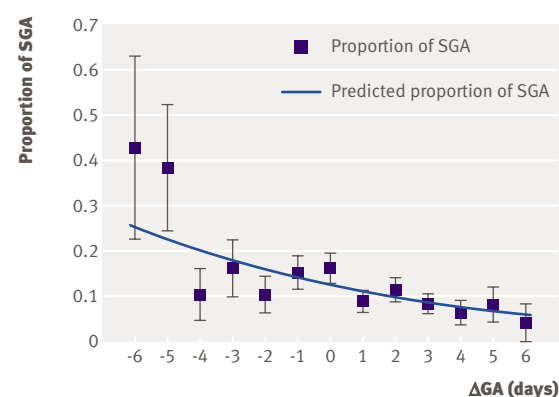

Fig 2 | Proportion of small for gestational age (SGA) neonates by size of ΔGA discrepancy (difference between observed and expected size of fetus in first trimester of pregnancy). Proportion (±SE) of SGA neonates and proportion of SGA neonates predicted by multivariable logistic regression are plotted by size of ΔGA discrepancy

Table 2 | Associations between observed minus expected size of fetus in first trimester (ΔGA) and birth weight, duration of pregnancy, and delivery of small for gestational age infant

Outcome	Unadjusted		Adjusted for maternal characteristics*		Adjusted for maternal characteristics* and pregnancy complications†	
	Coefficient/odds ratio‡ (95% CI)	P value	Coefficient/odds ratio‡ (95% CI)	P value	Coefficient/odds ratio‡ (95% CI)	P value
Birth weight (g)	28.2 (14.9 to 41.2)	‹0.0001	27.9 (14.6 to 41.2)	‹0.0001	27.9 (15.1 to 40.6)	‹0.0001
Duration of pregnancy (days)	0.42 (0.10 to 0.73)	0.009	0.48 (0.17 to 0.80)	0.003	0.49 (0.21 to 078)	0.001
Delivery of SGA infant	0.87 (0.81 to 0.94)	‹0.0001	0.88 (0.82 to 0.96)	0.002	0.90 (0.83 to 0.98)	0.013

SGA=small for gestational age.
*Maternal age; height; weight in first trimester; body mass index; race and ethnicity; number of previous term and preterm deliveries, miscarriages, and abortions; elevation above sea level; number of completed years of education; and fetal sex.
†Preterm delivery, pre-eclampsia, preterm premature rupture of fetal membranes, preterm labour, placental abruption, and placenta praevia.
‡Expressed for increase in ΔGA of 1 day.
Adjustment did not result in any statistically significant change in coefficients or odds ratios (all P›0.5 compared with unadjusted coefficient); goodness of fit tests showed no evidence of lack of fit (P›0.5 for all three logistic models).

WHAT IS ALREADY KNOWN ON THIS TOPIC

The size of a fetus in the first trimester of pregnancy is associated with its birth weight

This association has been suggested to be due to delayed ovulation rather than an association with slower first trimester growth

WHAT THIS STUDY ADDS

Fetal growth in the first trimester of pregnancy was strongly associated with birth weight in pregnancies with a known date of conception

Approximately half of this association was due to the effect of first trimester size on the duration of pregnancy and half on fetal growth in later pregnancy

The risk of delivering a small for gestational age infant is inversely related to first trimester growth

routinely collected data showed that fetuses that were smaller than expected in early pregnancy were at increased risk of adverse outcome, particularly poor growth. Intrauterine growth restriction was postulated to be evident in very early pregnancy.[6] However, other authors suggested that a prolonged interval between menstruation and conception was the determining factor.[7] Here we have shown that fetal growth in the first trimester of pregnancy is a major determinant of birth weight. Our study in pregnancies resulting from assisted reproductive technology has shown that the association between size in the first trimester and birth weight is not related to delayed ovulation but to first trimester growth.

The association between first trimester size and birth weight has now been shown in spontaneously conceived pregnancies[6] and in pregnancies resulting from assisted reproductive technology, with precisely known time of conception. The same finding in two different populations would be unlikely to result from other factors than a common underlying mechanism. Pregnancies with appropriate fetal growth in the first trimester, of which the observed and expected sizes were equal (ΔGA =0), had smaller birth weight and a higher risk of small for gestational age infants than the general population. This is presumably the result of impaired fetal growth occurring after the first trimester in pregnancies resulting from assisted reproductive technology.

Previous studies have also shown that early intrauterine growth restriction is associated with fetal abnormality, particularly aneuploidy.[14] The data used in our study were from a prospective cohort study of screening for Down's syndrome, in which aneuploidy was the primary outcome. We excluded all pregnancies with a fetal abnormality, and this cannot explain the observed association.

Birth weight and duration of pregnancy

Strong and statistically significant associations between ΔGA and both birth weight and the risk of delivering a small for gestational age infant persisted after adjustment for duration of pregnancy, a wide range of maternal characteristics, and complications of pregnancy. This suggests a major, independent effect of early pregnancy growth on both outcomes. Fetuses with a smaller than expected crown-rump

length may simply have been at an earlier stage of development. For example, if implantation and early embryonic development were delayed for a given assumed date of conception, the fetus would have a smaller than expected crown-rump length. However, delayed implantation would lead to both smaller than expected crown-rump length and apparently longer duration of pregnancy. In fact, we saw exactly the opposite association, and delayed implantation cannot explain the observed associations.

Implications

Measurement with ultrasound is recognised to be a more accurate method of estimating gestational age in the first trimester of pregnancy than menstrual dating, owing to errors in the assumed date of conception based on the last menstrual period. Therefore, for the purposes of intervention or screening, gestational age is adjusted on the basis of ultrasound criteria. However, our findings show that discrepancy in gestational age, where the time of conception is known, is related to the risk of delivering a small for gestational age infant. In women with a certain date of last menstrual period and a regular cycle and in women who conceive through assisted reproductive technology, pregnancies where the crown-rump length is smaller than expected may thus benefit from closer monitoring, especially for abnormalities of fetal growth.

These observations add to a growing body of evidence that duration of pregnancy and complications of late pregnancy may be the ultimate consequence of conditions in the very earliest stages of pregnancy.[15] [16] Adverse outcome of pregnancy in a considerable proportion of women is likely to be determined before their first prenatal visit. These findings underline the importance of detailed study of the periconceptional period and first trimester of pregnancy when assessing factors that influence the risk of adverse outcome and in the development of predictive tests.

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